REMARKS

Status of the claims

Claims 1 and 3-44 are pending in the present application. Claim 2 was previously cancelled and claims 5-9 and 14-44 previously withdrawn from consideration. In this amendment, claims 5-9 and 14-44 have been cancelled. Accordingly, claims 1, 3, 4, and 10-13 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Summary of Telephone Interview

Applicants would like to thank Examiner Channavajjala for extending the courtesy of a telephone interview with Applicant's representatives, Mika Mayer and Lisa Amii, on July 15, 2008. During the telephone interview, the rejection of claims 1, 3, 4, and 10-13 under 35 U.S.C. § 103(a) was discussed in view of Campbell (U.S. 5,962,532) and Wholehealthmd (www.wholehealthmd.com). Specifically, Applicant's representatives provided that a *prima facie* case of obviousness had not been established because: 1) Campbell teaches away from using a soapy water composition to remove capsaicin from the skin; and 2) that one of skill would not look to wash capsaicin from the skin (as described by Wholehealthmd) because the capsaicin composition of Campbell is injected into the body.

It was reiterated that Campbell teaches away from removing capsaicin by washing the skin with water because capsaicin is water insoluble (Merck Index, 14th Edition, p.1765), and thus, will not be removed with water. The Examiner was also reminded that data showing that capsaicin is also insoluble in warm soapy water (as disclosed by Wholehealthmd) was previously provided in Exhibit A of the Supplemental Amendment dated November 9, 2005 for this application. The data established that capsaicin is insoluble (less than 0.1% w/w) in warm soapy water at three different concentrations of antibacterial handsoap, even with frequent sonication over a 20 minute timeframe. A copy of the signed report describing the experiments that were performed to determine the solubility of capsaicin in warm soapy water (using Softsoap™ antibacterial handsoap) is attached

hereto. In view of this data, it was submitted that Campbell also teaches away from using warm soapy water to remove capsaicin from the skin.

Applicant's representatives also discussed how one of skill would not combine Campbell with Wholehealthmd because Campbell's composition is injected into the painful area (see, e.g., column 4, lines 14-18; column 4, lines 21-23; column 4, lines 51-55). Here washing the skin would have no effect. Thus, Campbell requires prior injection of an anesthetic to the area (see, e.g., column 4, lines 12-14) and administration of a narcotic analgesic for breakthrough pain (see, e.g., column 4, lines 46-51). It was pointed out that Campbell relieves the painful effect of capsaicin by treating the pain with another agent whereas Wholehealthmd is attempting to remove the cause of the pain. Based on the differing solutions provided to the problem of capsaicin's irritating and painful effects, it was submitted that one of skill would not combine the references.

In response, the Examiner stated that she would consider the arguments, but that it would also be helpful for her to review comparative data on Applicant's cleansing composition and other PEB-based soaps relating to capsaicin removal. Data obtained from experiments conducted with Applicant's cleansing composition may be found in Example 4 of the specification as originally filed (paragraphs 60-65), and is also attached hereto for the Examiner's convenience. A copy of a signed report describing experiments that were performed to determine the solubility of capsaicin in a PEG-containing composition (oily soil remover in U.S. 6,114,290 to Lyle, referred to as IGL-3 in the report) is also provided. This report states that IGL-3 was not found to dissolve at least 10% w/w capsaicin, as required by the claims.

In view of the above, withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 1, 3, 4, and 10-13 is respectfully requested. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

CONCLUSION

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 524522000500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: July 18, 2008

Respectfully submitted,

By _____
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Attachments: Example 4 (two pages)
PEG composition data from Amendment dated August 8, 2007 (four pages)
Exhibit A from Supplemental Amendment dated November 9, 2005 (six pages)

EXAMPLE 4

[0001] To determine the ability of cleansing gel to remove irritable substances from surfaces, a range of concentration of capsaicin solutions, in a volatile solvent, were applied to stainless steel coupons. Thin films of capsaicin (ranging from 4 μg to 16 μg per centimeter square) remaining on the surface of the steel coupons were equivalent to the maximum anticipated amount of capsaicin left on skin following clinical applications of 8% by weight capsaicin patches. The amount of cleansing gel used per square centimeter of surface, and application time were adapted from the clinical experience of cleansing gel usage.

Preparation of Capsaicin Solutions

[0002] A stock solution of capsaicin, in methanol, containing 103.1 mg/100mL capsaicin ((Lot F0010103) Formosa Laboratories, Taiwan) in a 100-mL volumetric flask, was prepared. The solution was clear and colorless. 10 mL each of four concentrations of capsaicin solutions 0.4 mg/mL, 0.3 mg/mL, 0.2 mg/mL and 0.1mg/mL were prepared from above stock solution.

Cleaning of Steel Coupons Exposed to Capsaicin Solutions

[0003] Four steel coupons, 5 cm x 5 cm each, (316 SS Finish from Globe Pharma) were rinsed with methanol and allowed to dry completely. 1 mL of 0.1 mg/mL capsaicin solution was slowly applied to a coupon at about 40°C (on a hot plate) such that methanol evaporated without solution dribbling from the edges.

[0004] For these experiments, a cleansing gel with the following components was used:

Component	% (w/w)
Carbowax PEG 300 (Polyethylene Glycol 300)	89.08
Carbopol 1382	1.00
Versene NA (Edetate Disodium)	0.10
Sodium Hydroxide, 10% solution	0.30
Butylated Hydroxyanisole	0.02
Purified Water	9.50

[0005] The dried coupon was smeared with 1 mL of cleansing gel which was removed after one minute with a single pre-washed swab (which was also used to apply cleansing gel). The collected gel along with the swab was added to a pre-washed scintillation vial containing a small magnetic stirrer. 9 mL methanol was added and the sample was stirred for 10 minutes. Three

more samples were prepared in similar fashion using 0.4 mg/mL, 0.3 mg/mL and 0.2 mg/mL capsaicin solutions. TABLE 5 describes the percent capsaicin recovery from four samples containing different initial capsaicin amounts.

TABLE 5

Percent Recovery of Capsaicin

Sample ID (mg/mL)	UV Absorbance at 281 nm	Adjusted Absorbance[1]	Capsaicin Concentration of Recovered Solution[2]	Amount Capsaicin Recovered[3] (mg)	Amount Capsaicin Applied[4] (mg)	Percent Capsaicin Recovery
0.10	0.212	0.156	0.011769	0.11769	0.1	117.7
0.20	0.261	0.205	0.016818	0.16818	0.2	84.1
0.30	0.302	0.246	0.021042	0.21042	0.3	70.1
0.40	0.415	0.359	0.032684	0.32684	0.4	81.7

[1] Adjusted Abs. = Abs - subtraction factor (0.056)
[2] Concentration = (Adjusted Abs.-Y intercept)/slope [from linear curve in figure 2]
[3] Amount Recovered = Concentration x vol of solution containing recovered gel (i.e. 10mL)
[4] Amount of capsaicin in one mL of application solution

As the results in Table 3 indicate, the cleansing gel achieved an average of 88.4% capsaicin recovery. In the case of 0.1 mg/mL capsaicin concentration, experimental error appears to have led to a higher number (i.e. 117.7 %). Exclusion of this data point shifts the average percent recovery down to 78.6% removal of residual amounts of capsaicin from an inert surface.

SOLUBILITY ANALYSES
OF
CAPSAICIN
IN CLEANSING GEL AND IGL-3

Study No. 007-00985

Study Conducted By
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Final Report: June 26, 2007

SOLUBILITY OF CAPSAICIN IN IGL-3 AND CLEANSING GEL
(STUDY NO. 007-00985)

I. OBJECTIVE:

To test and compare the ability of Cleansing Gel and IGL-3 (Example No.3 in US Patent 6,114,290) formulations to dissolve 10% w/w capsaicin at room temperature

II. FORMULATION COMPOSITION

IGL-3: Percent Composition

Formulation ID	Ingredients					
	A	B	C	D	E	F
	PEG-400	Glycerol	Carbopole ETD2020	Triethanolamine	Methylchloroisothiazolinone + Methylisothiazolinone	Water
	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
IGL-3	30	30	1.33	0.38	0.05	38.24

IGL-3: Composition in Grams to Prepare 30 Grams

Formulation ID	Ingredients					
	A	B	C	D	E	F
	PEG-400	Glycerol	Carbopole ETD2020	Triethanolamine	Methylchloroisothiazolinone + Methylisothiazolinone	Water
	g	g	g	g	g	g
IGL-3	8.9950	9.0281	0.4006	0.4227	0.019	11.4750

III. METHOD OF PREPARATION

1. Prepared Solution E as follows:
   a. Added 4.2 mL of 5-Chloro-2-methyl- 4 isothiazolin-3-one solution to 50mg of 2-Methyl-4-isothiazolin-3-one hydrochloride.
   b. Added 2.5 mL of Dionized water and mix to make a 1.5% solution
2. Dispersed Carbopole (C) in water (F) under high sheer mixing.
3. Added PEG-400 (A), Glycerol (B) and preservatives (E) above solution and mix.
4. Adjusted pH to 7.0 by slowly adding triethanolamine (D)

IV. SOLUBILITY DETERMINATION

Solubility of capsaicin was determined as follows:

IGL-3

1. Weighed 500 mg of capsaicin in a Liquid Scintillation Vial.

2. Add 5 grams of test formulation, prepared in section III, to the above Vial containing 500 mg of capsaicin. Vortexed the contents of the vial for 10 minutes. Following vortexing any capsaicin crystals un-wetted by the gel were mixed in mechanically using a metal spatula.

3. Visually inspected to see if any crystals are left undissolved. In addition, the sample was stirred for 5 seconds, and then a small aliquot of gel was smeared on microscope glass slide, and observed under microscope. Recorded observations about the presence or absence of crystals on the glass slide in Table 1.

Cleansing Gel

1. Weighed 500 mg of capsaicin in a Liquid Scintillation Vial.

2. Added 5 grams of Cleaning Gel, provided by NeurogesX, to the above Vial containing 500 mg of capsaicin. Vortexed the contents of the vial for 10 minutes. Following vortexing any capsaicin crystals un-wetted by the gel were mixed in mechanically using a metal spatula.

3. Visually inspected to see if any crystals are left undissolved. In addition, a small aliquot of gel was smeared it on microscope glass slide, and observed under microscope. Recorded observations about the presence or absence of crystals on the glass slide in Table 1.

V. SUMMARY OF SOLUBILITY DATA AND OBSERVATIONS

Table 1. Solubility Comparison and Observations

	SOLUBILITY DATA	
	IGL-3	**Cleansing Gel**
Did formulation dissolve 10% w/w capsaicin at room temperature after 10 minutes mixing?	No	Yes
Describe observations under microscope, if applicable.	Crystals were clearly visible both with/ or without the microscope.	Only the crystals that were present in the Cleansing Gel itself were seen. No Capsaicin crystals were seen.

VI. RESULTS AND DISCUSSION

The IGL-3 formulation was much more viscous than the Cleansing Gel. The amounts recorded were the actual amounts used for the preparation and differ slightly from the theoretical amounts. The amount of Triethanolamine used was almost 4 times the theoretical amount of 0.114g (for a 30g preparation). The IGL-3 formulation was very viscous at this point and the pH adjustment was performed by adding the triethanolamine dropwise and stirring using the pH probe. The high viscosity of the formulation is suspected as why additional triethanolamine was required to reach a final pH of 7.0. The IGL-3 formulation contained many entrapped air bubbles but no crystals. This made the formulation somewhat opaque. An attempt was made to remove the air bubbles both by stirring and by placing the formulation under vacuum for 5 minutes. Neither procedure removed air bubbles. The original sample of Cleansing Gel contained crystals that look different from the capsaicin crystal seen in IGL-3 formulation The IGL-3 Formulation crystals appeared as small fairly regular diamond shapes some of which contained small crosses inside the crystal. They were widely dispersed throughout the gel. The capsaicin crystals were larger and more irregular in form roughly square to rhomboid in shape. They appeared to clump together in groups. Inside the crystals was an assortment of squiggly lines. After the addition on the IGL-3 the number and clumping of the capsaicin crystals was reduced but their form and appearance remained the same. The addition of capsaicin and its subsequent dissolution in Cleansing Gel seemed to reduce the number of crystals originally present in the sample.

Testing performed by: **Robert Almond** Signature: _____ Date: 6/18/2007

Read and understood by: **Michael J. Swickard** Signature: _____ Date: 6/26/2007

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EXHIBIT A

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Approximate Solubility Analyses of Capsaicin

Filename SR-20050857.02

Project Id EA20051109

*A revised report generated for NeurogesX on 11/4/2005**

Prepared by: Brenton W. Russell 04 Nov 2005
Brenton W. Russell, Manager, Date

Reviewed by: Daniel K. Pannell 11/4/05
Daniel K. Pannell, Ph.D, Director, Date

** In accordance with cGMP regulations, all reports and data are generated using SSCI Standard Operating Procedures unless otherwise specified*

TABLE OF CONTENTS

I. INTRODUCTION

NeurogesX Inc. submitted one sample of capsaicin for solubility determination in three concentrations of soapy water. This report summarizes the results.

This revised report is being issued to provide more detail for each of the approximate solubility experiments [1,2].

II. EXPERIMENTAL

Approximately 5 – 6 mg of capsaicin was weighed into each of three flasks, and aliquots of mixtures of handsoap (Softsoap Antibacterial, Colgate-Palmolive, lot 5268506) in tap water were added to the flask. Between additions, the mixture was sonicated. The elapsed time of the experiments were not documented, however it is the analyst's recollection that each approximate solubility test took about 20 minutes.

Solubility was estimated from the total volume of solvent used to obtain a clear solution at the time of the addition of the aliquots, as determined by visual inspection. Note that actual solubilities may be greater than those calculated due to slow rates of dissolution. If complete dissolution did not occur during the experiment, the solubility is expressed as "less than". Values are reported to the nearest 0.1 mg/mL.

III. RESULTS AND DISCUSSION

For sample 2226-65-01, fifty-five 500-μL aliquots of soapy water (containing 1 pump of soap) were added to 5.1 mg of capsaicin with frequent sonication. Particles persisted and the sample was foamy at the surface. Forty-five more aliquots 500-μL aliquots were added. A few particles persisted after sonication. The sample was capped and set aside. After standing at room temperature overnight, the sample was found to be completely dissolved.

For sample 2226-65-02, ten 1000-μL aliquots of soapy water (containing 2 pumps of soap) were added to 5.2 mg of capsaicin with sonication. Solids persisted. This addition of ten 1000-μL aliquots was repeated four times, with sonication after each addition, for a total of 5000 μL. Solids persisted and the sample was capped and set aside. After standing at room temperature for six days, the sample was found to be completely dissolved.

For sample 2226-65-03, ten 1000-μL aliquots of soapy water (containing 3 pumps of soap) were added to 5.8 mg of capsaicin with sonication. Solids persisted. This addition of ten 1000-μL aliquots was repeated four times, with sonication after each addition, for a total of 5000 μL. Solids persisted and the sample was capped and set aside. After standing at room temperature for six days, the sample was found to be nearly all dissolved.

Table 1 summarizes the approximate solubility experiments for capsaicin lot AE03857. Immediately following each addition of solvent and the subsequent sonication, each of the three

soapy water mixtures failed to dissolve a relatively small amount of capsaicin, meaning the immediate (short-term) solubility is less than 0.1 mg/mL. According to the current USP classification of solubility [3], the sample is considered to be insoluble in all three soapy mixtures. This is consistent with the original results in the preliminary polymorph screen that predicted capsaicin to be insoluble in water [4].

Because two of the samples became fully dissolved after an extended period of time (with 1 and 2 pumps of soap), the equilibrium solubility is greater than or equal to approximately 0.1 mg/mL for those samples. For the sample where 3 pumps of soap were used, the sample nearly all dissolved, meaning the equilibrium solubility was nearly equal to approximately 0.1 mg/mL.

IV. REFERENCES

1. Report from SSCI to NeurogesX, *Approximate Solubility Analyses of Capsaicin*, SR-20050857.01, 10/28/05.
2. Contact Report for NeurogesX, CR-11544.01, 11/4/05
3. United States Phamacopoeia, National Formulary, General Notices, USP28/NF23, January 1, 2005.
4. SSCI Report to NeurogesX Inc., *Preliminary Polymorph Screen of Capsaicin*, SR-20030453.03, dated 12/19/2003.

V. TABLES

Table 1. Approximate Solubilities of Capsaicin Lot AE03857 (SSCI LIMS 80960)

Amount of Capsaicin (mg)	Amount of soap (g/50 mL)	Approximate Short-Term Solubility [a]	Approximate Long-Term Solubility [a]	Solubility (descriptive) [b]	Notebook Reference
5.1	1.2295 (1 pump)	< 0.1 mg/mL	≥0.1 mg/mL	insoluble	2226-65-01
5.2	3.2867 (2 pumps)	< 0.1 mg/mL	≥0.1 mg/mL	insoluble	2226-65-02
5.8	5.0979 (3 pumps)	< 0.1 mg/mL	≤0.1 mg/mL	insoluble	2226-65-03

a. Solubilities are calculated based on the total solvent used to give a solution; actual solubilities may be greater because of a slow rate of dissolution. Solubilities are reported to the nearest 0.1 mg/mL.

b. Descriptive solubility from U. S. Pharmacopoeia, National Formulary, General Notices, page 9, USP 28/NF 23, Jan 1, 2005. See notebook 2205-21 for calculations to parts solvent required for 1 part solute.